54. (Amended) The isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51, wherein said neurotrophic variant comprises amino acids 33-666 of SEQ ID NO:34.

55. (Amended) The isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51, wherein said neurotrophic variant has at least 90% amino acid sequence identity with amino acid residues 33-666 of SEQ ID NO:34.

B8 cont'd

56. (Amended) A composition, comprising the isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51 and a physiologically acceptable carrier.

B9

58. (Amended) The composition of Claim 57, wherein said mammalian neurotrophic factor is ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF).

REMARKS

Claims 34-39 have been canceled and Claims 25-27, 29, 30, 32, 42-44, 46, 47, 49, 51-56 and 58 have been amended. Claims 25-33 and 42-58 are pending.

Claim 25 has been amended to include an exclusionary proviso. With regard to such a proviso, the MPEP instructs "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." (MPEP § 2173.05(i), citing In re Johnson, 194 USPQ 187, 196 (CCPA 1977).) The application positively recites SEQ ID NO:34 throughout the specification, in Figure 26C and the Sequence Listing. Accordingly, the application provides support for the proviso.

Claim 25 has been further amended, and Claims 26, 27, 30, 42-44, 47 and 51-56 have been amended to recite "isolated neurotrophic peptide."

Claims 29, 32, 46, 49 and 58 have been amended to recite "wherein said mammalian neurotrophic factor is ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF)."

Claim 51 has been amended to more particularly point out the claimed subject matter.

Support for the amended claims is found throughout the application as filed, for example, at page 21, lines 16-20; Figure 26C; page 4, lines 6-9; and page 29, lines 2-5. The amended

claims are supported by the application as filed. Therefore, this Amendment adds no new matter. Further remarks are presented below with reference to the numbered paragraphs in the Office Action.

Paragraph 3. Restriction

Applicants' thank the Examiner for reconsidering the restriction requirement and examining Claims 25-33 and 42-50 on the merits. With regard to Claims 51-58, the Examiner states that these claims are not drawn to elected SEQ ID NO:14. (Office Action at page 2, lines 13-21.) Reconsideration and rejoinder of Claims 51-58 is requested in view of the following.

Claim 51 is drawn to a neurotrophic variant of SEQ ID NO:34, and as originally filed recited that the variant comprises the amino acid sequence of SEQ ID NO:14. Claim 34 further defined the neurotrophic variant as having fewer amino acid residues that SEQ ID NO:34, and as having at least 90% amino acid sequence identity with a corresponding portion of SEQ ID NO:34.

The language of Claim 58 has been amended to more clearly point out the claimed subject matter, and now more clearly indicates that the neurotrophic variants encompassed by the claim comprise the amino acid sequence set forth in SEQ ID NO:14. The claimed neurotrophic variants can contain additional amino acids, provided that the variant has fewer amino acids than SEQ ID NO:34 and that the variant has at least 90% amino acid sequence identity with the corresponding portion of SEQ ID NO:34. Accordingly, when the amino acid sequence of a claimed variant is aligned with SEQ ID NO:34, the variant sequence will include a region that is identical to residues 379-394 of SEQ ID NO:34 (SEQ ID NO:14) and will be at least 90% identical to SEQ ID NO:34 over the length of the variant sequence. Claims 52-55 further limit the variant of Claim 51 by reciting that the variant comprises particular amino acid sequences that are longer than SEQ ID NO:14.

In view of the foregoing, Applicants believe that it is clear that Claims 51 through 58 read on the elected SEQ ID NO:14, and respectfully request reconsideration and rejoinder of Claims 51 through 58.

Paragraph 6. Rejection of Claims 25-33 and 42-50 Under 35 U.S.C. § 101

Claims 25-33 and 42-50 are rejected under 35 U.S.C. § 101 as being drawn to non-statutory subject matter. The Examiner states that the claims read on a product of nature and suggests that the claims be amended to recite "an isolated …". (Office Action at page 3, lines 11-13.)

The claims have been amended as suggested by the Examiner, thereby obviating the rejection.

Paragraph 8. Rejection of Claims 25 and 27 Under 35 U.S.C. § 102(b)

Claims 25 and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Pereira *et al.* (*J. Exp. Med. 174*:179-191 (1991); Reference AX of record). The Examiner states that Pereira *et al.* (AX) teaches *T. cruzi* neuraminidase having a sequence corresponding to a peptide comprising SEQ ID NO:14 with 100% identity. (Office Action at page 4, lines 3-5.)

Pereira *et al.* (AX) teaches the nucleotide sequence of the Clone 7F open reading frame encoding *T. cruzi* neuraminidase, and the deduced amino acid sequence of the protein encoded by Clone 7F. (AX at page 183, left column and Figure 3.). The nucleotide sequence of Clone 7F and the amino acid sequence of the neuraminidase encoded by Clone 7F are disclosed in the application. (See, *e.g.*, Figures 26A-C, SEQ ID NO:33 and SEQ ID NO:34.) Claim 25 has been amended to recite "with the proviso that said isolated neurotrophic peptide is not SEQ ID NO:34." As amended, Claims 25 and 27 do not read on the *T. cruzi* neuraminadase (Clone 7F) disclosed in Pereira *et al.* (AX) and are not anticipated. Reconsideration and withdrawal of the rejection are requested.

Paragraph 9. Rejection of Claims 25, 27, 30 and 33 Under 35 U.S.C. § 102(a) or 35 U.S.C. § 103(a)

Claims 25, 27, 30 and 33 are rejected under 35 U.S.C. § 102(a) as being anticipated by, or in the alternative under 35 U.S.C. § 103(a) as obvious over Chuenkova *et al.* (*Biochem. & Biophys. Res. Comm. 262*:549-556 (1999); Reference AZ of record). The Examiner states that Chuenkova *et al.* teaches a trans-sialidase from *T. cruzi* that has neuraminidase activity and sialyl-transferase activity, and teaches various deletion and fusion mutants of the protein that

have sequences that differ from the wild-type form of the protein. (Office Action at page 4, lines 14-20.) The Examiner acknowledges that Chuenkova *et al.* does not disclose the amino acid sequence of the *T. cruzi* trans-sialidase. (Office Action at page 4, lines 22-23.) However, the Examiner states that the record is insufficient to determine whether or not the claimed proteins are inherently the same as or obvious over the proteins disclosed in Chuenkova *et al.* because the Examiner cannot determine how the proteins differ. (Office Action at page 5, lines 3-12.) The Examiner relies on In re Best to shift the burden to Applicants to establish that the claims are neither anticipated by nor obvious over Chuenkova *et al.* (Office Action at page 5, lines 11-12.)

Chuenkova *et al.* teaches that certain deletion mutants of *T. cruzi* transialidase were prepared and that the trans-sialidase and neuraminidase activities of the mutants were assessed. (Chuenkova *et al.* at page 553, Fig. 2.) In the "EXPERIMENTAL PROCEDURES" section, Chuenkova *et al.* teaches that the 19y-clone of *T. cruzi* trans-sialidase was obtained from a genomic DNA library and that the deletion mutants were constructed using the 19y clone. (Chuenkova *et al.* at page 550, paragraphs titled *Bacterial strains and plasmids* and *Construction of the mutants*.) Thus, Chuenkova *et al.* teaches deletion mutants of the Clone 19y trans-sialidase. Chuenkova *et al.* does not teach that any of the disclosed mutants have neurotrophic activity.

Anticipation

Claims 25, 27, 30 and 33 are not anticipated by Chuenkova *et al.* because the neurotrophic peptides encompassed by these claims have amino acid sequences that comprise the amino acid sequence of SEQ ID NO:14, while the Clone 19y trans-sialidase and deletion mutants of Chuenkova *et al.* do not contain the amino acid sequence of SEQ ID NO:14. The Examiner's attention is directed to the Exhibit which shows an alignment of the amino acid sequences of Clone 19y trans-sialdase (SEQ ID NO:2; labeled "Query") and Clone 7F trans-sialidase (SEQ ID NO:34; labeled "Sbjct"). The alignment was prepared using the Blast 2 Sequences algorithm with default parameters.

The alignment reveals that the amino acid sequences of the Clone 19y and Clone 7F trans-sialidases are not identical, and that the sequences are divergent in the area that corresponds to SEQ ID NO:14 (residues 379 to 394 of SEQ ID NO:34 (Clone 7F), residues 457-471 of SEQ

ID NO:2 (Clone 19y)). This region is highlighted in yellow on the Exhibit and is reproduced below.

R Q R L P K R M G G S Y R C	SEQ ID NO:14
R Q R L P K R M - G G S Y R C	residues 379-394 of SEQ ID NO:34 (Clone 7F)
S G N A S Q N V W E D A Y R C	residues 457-471 of SEQ ID NO:2 (Clone 19y)

The alignment demonstrates that the Clone 19 trans-sialidase does not contain the amino acid sequence of SEQ ID NO:14, and that only 3 of 15 amino acids in this region (underlined above) of Clone 19y are identical (~20% identity) to the corresponding amino acids in Clone 7F or SEQ ID NO:14. Accordingly, Claims 25, 27, 30 and 33 do not read on the Clone 19y trans-sialidase or the deletion mutants disclosed in Chuenkova *et al.* and are not anticipated.

Obviousness

With regard to the alternative rejection under 35 U.S.C. § 103, it is well established that a finding that the claimed invention is obvious requires that (1) "the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process;" and (2) that "the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. With regard to the requisite suggestion or motivation, it is insufficient that the disclosure of a reference can be modified; to render the result of the modification obvious, the prior art must suggest the desirability of the modification. In re Mills, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).

Claims 25, 27, 30 and 33 are not obvious over Chuenkova *et al.*, because the reference does not disclose any proteins that contain the amino acid sequence of SEQ ID NO:14 or disclose any proteins that contain an amino acid sequence that has at least 90% identity to SEQ ID NO:14. In addition, the reference does not contain any teaching or suggestion that the disclosed mutants

could or should be altered to contain SEQ ID NO:14 or an amino acid sequence that has at least 90% identity thereto. Moreover, Chuenkova *et al.* does not teach or suggest that *T. cruzi* trans-sialidase or any fragments or mutants of the protein would have neurotrophic activity. Accordingly, the reference fails to provide both the requisite suggestion or motivation to attempt to prepare the claimed polypeptides, which comprise the amino acid sequence of SEQ ID NO:14 and have neurotrophic activity, and also fails to provide a reasonable expectation of success in obtaining the claimed peptides.

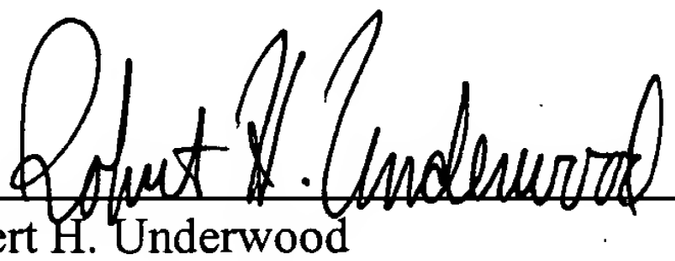
In view of the foregoing, reconsideration and withdrawal of the rejection are requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 
Robert H. Underwood
Registration No. 45,170
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: July 29, 2003

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Claims 34-39 have been canceled without prejudice.

25. (Twice Amended) [~~A~~] An isolated neurotrophic peptide, comprising the amino acid sequence of peptide C14 (SEQ ID NO:14) or a neurotrophic variant of SEQ ID NO:14, wherein said neurotrophic variant has at least 90% amino acid sequence identity to SEQ ID NO:14, with the proviso that said isolated neurotrophic peptide is not SEQ ID NO:34.

26. (Twice Amended) The isolated neurotrophic peptide of Claim 25, further comprising an amino-terminal protecting group, a carboxyl-terminal protecting group, or an amino-terminal protecting group and a carboxyl-terminal protecting group.

27. (Amended) A composition, comprising the isolated neurotrophic peptide of Claim 25 and a physiologically acceptable carrier.

29. (Twice Amended) The composition of Claim 28, wherein said mammalian neurotrophic factor is [~~CNTR of LIF~~] ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF).

30. (Amended) A fusion protein, comprising the isolated neurotrophic peptide of Claim 25 and a fusion partner.

32. (Amended) The fusion protein of Claim 31, wherein said neurotrophic factor is [~~CNTF or LIF~~] ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF).

42. (Amended) The isolated neurotrophic peptide of Claim 25, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:12 and SEQ ID NO:13.

43. (Amended) The isolated neurotrophic peptide of Claim 42, further comprising an amino-terminal protecting group, a carboxyl-terminal protecting group, or an amino-terminal protecting group and a carboxyl-terminal protecting group.

44. (Amended) A composition, comprising the isolated neurotrophic peptide of Claim 42 and a physiologically acceptable carrier.

46. (Amended) The composition of Claim 45, wherein said mammalian neurotrophic factor is ~~[CNTF or LIF]~~ ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF).

47. (Amended) A fusion protein, comprising the isolated neurotrophic peptide of Claim 42 and a fusion partner.

49. (Amended) The fusion protein of Claim 48, wherein said mammalian neurotrophic factor is ~~[CNTF or LIF]~~ ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF).

51. (Amended) [~~A~~] An isolated neurotrophic variant of SEQ ID NO:34, wherein said variant comprises [~~comprising~~] the amino acid sequence of SEQ ID NO:14, [~~wherein said variant~~] comprises fewer amino acid residues than SEQ ID NO:34 and has at least 90% amino acid sequence identity with a corresponding portion of SEQ ID NO:34.

52. (Amended) The isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51, wherein said neurotrophic variant comprises SEQ ID NO:13.

53. (Amended) The isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51, wherein said neurotrophic variant comprises amino acids 79-666 of SEQ ID NO:34.

54. (Amended) The isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51, wherein said neurotrophic variant comprises amino acids 33-666 of SEQ ID NO:34.

55. (Amended) The isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51, wherein said neurotrophic variant has at least 90% amino acid sequence identity with amino acid residues 33-666 of SEQ ID NO:34.

56. (Amended) A composition, comprising the isolated neurotrophic variant of SEQ ID NO:34 according to Claim 51 and a physiologically acceptable carrier.

58. (Amended) The composition of Claim 57, wherein said mammalian neurotrophic factor is ~~[CNTF or LIF]~~ ciliary neurotrophic factor (CNTF) or leukemia inhibitory factor (LIF).